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Peripheral arteriovenous malformations: diagnosis and future prospects

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Abstract

Peripheral arteriovenous malformations (AVMs) are rare, high-flow vascular anomalies caused by errors in vasculogenesis or angiogenesis, frequently driven by mutations in the RAS/RAF/MEK/ERK signaling pathway. These lesions exhibit progressive behavior, leading to diverse clinical presentations ranging from localized pain, swelling and important bleeding to severe systemic complications such as high-output cardiac failure. AVMs pose significant diagnostic and therapeutic challenges due to their heterogeneous nature and high recurrence rates.

Accurate diagnosis relies on advanced imaging modalities, including Doppler ultrasonography, magnetic resonance imaging and angiography, and digital subtraction angiography, which provide critical insights into lesion extent and flow dynamics. Current management strategies involve a combination of preoperative embolization, surgical excision, and endovascular therapies. However, incomplete treatment frequently results in recurrence, emphasizing the need for complete nidus removal. Emerging antiangiogenic therapies, such as thalidomide and MEK inhibitors, show promise as adjuncts to invasive treatments, potentially reducing recurrence rates and enhancing long-term outcomes.

This review highlights the need for standardized treatment protocols, integrating clinical, anatomical, and genetic insights. Syndromic AVMs require broader diagnostic and therapeutic considerations, while advances in molecular genetics pave the way for targeted pharmacologic therapies. Future research should focus on refining combination therapies and optimizing individualized care through multidisciplinary approaches. While challenges remain, these developments represent significant steps toward improving outcomes for patients with this complex and debilitating vascular anomaly.

Keywords : Arteriovenous malformation, high-flow vascular malformation, vascular anomaly.

Introduction

Arteriovenous malformations (AVMs) are vascular anomalies resulting of abnormal vasculogenesis or angiogenesis, forming high-flow vascular lesions characterized by direct connections between arteries and veins, bypassing the capillary bed. These anomalies represent a rare and complex subset of vascular lesions with unique clinical and pathological features. Due to their rarity and the lack of comprehensive registries, the precise incidence of AVMs remains unclear. Intracranial AVMs, involving brain structures, are significantly more common, occurring up to 20 times more frequently than their extracranial counterparts(1,2). Consequently, intracranial AVMs have been more extensively studied, whereas extracranial AVMs have been estimated with an incidence ranging between 5 and 613 cases per 100,000 individuals(3,4).

AVMs are a heterogeneous group of high-flow vascular lesions. The ISSVA (International Society for the Study of Vascular Anomalies) classification distinguishes direct arteriovenous fistulas (AVFs) from more complex nidal vessel entanglements, referred to as AVMs(5). While AVFs can be considered a subtype of AVMs, the broader term encompasses all high-flow lesions. This concept will be adopted throughout this review.

Although usually congenital, AVMs often remain undiagnosed until later in life, with symptoms frequently emerging following trauma or during hormonal shifts, such as puberty. They can develop anywhere in the body and exhibit progressive growth over time. These lesions can lead to important deformities, significant pain, ulceration, severe bleeding causing chronic anemia, or impaired organ function, depending on their size and anatomical location. Therefore, the VASCERN-VASCA classification system further subdivides AVMs based on their anatomical location(6). According to this system, AVMs are categorized as follows: 1) central nervous system AVMs, 2) visceral or pelvic AVMs, and 3) peripheral AVMs. This review will focus exclusively on peripheral AVMs.

Physiopathology and Genetics

AVMs are believed to arise from vasculogenesis errors during embryonic development, classifying them as congenital vascular anomalies(7). However, this congenital origin is challenged by the observation of acquired arteriovenous fistulas (AVFs) in the central nervous system following venous thrombosis(8,9). Whether peripheral AVMs can also be acquired remains a topic of debate. What is more certain is that AVMs are inherently progressive due to abnormal angiogenesis(10), with the potential to invade surrounding healthy tissues over time. While the natural progression of these lesions is well-documented, the precise mechanisms underlying this evolution remain poorly understood. Endothelial cells (ECs) within AVMs exhibit exaggerated responses to hypoxia(11) and shear stress(12), contributing to their dynamic behavior.

Sporadic AVMs are primarily associated with gain-of-function mutations within the RAS/RAF/MEK/ERK signaling pathway (**Fig 1**). Among these, mutations in the *MAP2K1* gene, encoding for MEK which plays a crucial downstream role in this pathway, have been identified as a key driver of these vascular anomalies(13,14). In the facial region, distinct phenotypes have been observed based on the underlying mutation: *MAP2K1*-mutated AVMs seem to differ from those with *KRAS* mutations, with the latter often being associated with more severe and extensive clinical presentations(14). While *MAP2K1* and *KRAS* mutations account for most extracranial AVMs, mutations in *BRAF*, *HRAS*, and *RIT1* have also been documented in sporadic cases(14–17).

Although AVMs are typically isolated and sporadic, approximately 30% of cases occur as part of syndromic presentations(18). These syndromes may be hereditary or sporadic in nature(6). For instance, loss-of-function (LoF) mutations in the *RASA1* gene are associated with Capillary Malformation–Arteriovenous Malformation 1 (CM-AVM 1)(19–21), while LoF mutations in the *EPBHB4* gene underlie CM-AVM 2(22,21). Additionally, LoF mutations in *PTEN* are implicated in AVMs within the context of *PTEN* Hamartoma Tumor Syndrome (PHTS)(23).

Clinical Presentation

AVMs exhibit a wide range of clinical manifestations, predominantly influenced by their anatomical location and the tissues involved(6). Common presenting symptoms include pain, swelling, bleeding, redness, and the presence of a abnormal palpable artery or even a thrill, all indicative of the high-flow nature of these lesions. These signs are critical for raising clinical suspicion of AVMs. As these malformations progress, systemic complications such as high-output cardiac failure may arise due to the increased circulatory demands imposed by arteriovenous shunting.

The Schöbinger Classification categorizes AVMs into four clinical stages, guiding diagnosis and management. Stage I represents quiescent lesions characterized by warmth and erythema. Stage II lesions, in the expansion phase, show pulsations, thrills, and bruits. Stage III marks complications such as pain, ulceration, bleeding, or deformation, while Stage IV reflects advanced stages with cardiac failure(24), as illustrated in **Fig 2**.

AVMs demonstrate a strong predilection for the craniofacial region, with approximately 50% of cases involving the head and neck. Within this area, the cheek and ear are particularly common sites(24). The morphological presentation can vary considerably. Simple forms may manifest as solitary AVFs or a single nidus with one or more feeding arteries, sometimes with extensive tissue involvement. In contrast, others may mimic capillary malformation or infantile hemangioma, complicating the differential diagnosis(25).

These lesions frequently infiltrate adjacent tissues, leading to diverse symptoms. Cutaneous involvement often manifests as areas of warmth and visible erythema. Due to their high-flow dynamics, complications such as pain, ulceration and bleeding are common. Ulceration may result from tissue ischemia due to the vascular shunt or venous hypertension in the affected region(7). Mucosal AVMs are prone to recurrent bleeding episodes, while primary bone AVMs predominantly affect the maxillofacial skeleton, with a unique predilection for teeth-bearing bones(24).

Natural Evolution and Impact of Hormonal Changes

Extracranial AVMs are classified as congenital vascular anomalies(7), with around 40% diagnosed at birth and 60% diagnosed during early childhood(1,26). Puberty marks the onset of clinical symptoms in 15–20% of cases, while approximately 20% first present during adulthood(1,24). Despite their probable congenital origin, external factors frequently contribute to their clinical manifestation or progression. For example, trauma precipitates AVM progression in approximately 2.5% of cases(24). This finding supports the theory that AVMs may remain asymptomatic or minimally symptomatic until an external event triggers their progression. Hormonal changes significantly influence AVM progression, particularly during puberty and pregnancy. Puberty precipitates clinical symptoms in 10–15% of cases, while pregnancy exacerbates AVMs in 25–50% of cases(1,2,26,27). Childhood-diagnosed AVMs are highly dynamic, with approximately 40% progressing before puberty and 80–84% exhibiting further progression by adulthood(1,2,26).

Syndromic Associations

Syndromic AVMs are less common but present distinct clinical challenges. CM-AVM features atypical capillary malformations surrounded by pale halos, often in conjunction with fast-flow lesions (AVMs or AVFs)(21,20,28,22). Parkes-Weber Syndrome (PKWS), considered as part of the CM-AVM spectrum, is characterized by limb hypertrophy, capillary malformations, and fast-flow lesions(29). PHTS encompasses multiple syndromes combining hamartomas, overgrowth, and increased cancer risk, occasionally associated with AVMs(23). Facial AVMs may co-occur with intracranial fast-flow lesions in Cerebrofacial Arteriovenous Metameric Syndrome (CAMS). Similarly, dorsal AVMs may be part of Spinal Arteriovenous Metameric Syndrome (SAMS), combining spinal and dorsal AVMs in a metameric distribution(6).

Diagnostic Evaluation

The diagnosis of AVMs begins with a comprehensive physical examination, particularly for lesions with superficial components. Physical findings provide critical information about the lesion's size, location, and surface characteristics. However, physical examination alone is limited in characterizing deeper lesions, assessing flow dynamics, and delineating the full anatomical extent. Accurate diagnosis and effective management planning require a combination of clinical assessment and advanced imaging modalities, as illustrated in **Fig 3**.

Doppler ultrasonography (Doppler US) is a practical, non-invasive, and cost-effective tool in the initial diagnostic work-up of AVMs. It is particularly advantageous because it avoids ionizing radiation (30). Gray-scale ultrasonography serves as an initial step, allowing for the assessment of lesion depth and extent (30,31). The hallmark feature of AVMs-a nidus of turbulent, multidirectional flow-is effectively visualized with color Doppler imaging(30). Spectral Doppler analysis provides quantitative insights into blood flow dynamics, including parameters such as flow velocities and vascular resistance (30,31). Key diagnostic markers of high-flow vascular anomalies include abundant flow signals ($\geq 8/cm^2$), elevated systolic velocities (>20 cm/s), a low resistance index (<0.50), and arterialization of venous outflow (31,32). Despite its utility, Doppler US is less effective for evaluating deep or complex lesions and is heavily dependent on operator expertise, which can limit reproducibility and consistency in longitudinal assessments.

Magnetic resonance imaging (MRI) is considered the imaging modality of choice for a detailed and comprehensive evaluation of AVMs due to its superior soft tissue contrast and reproducibility (30). T1-weighted non-contrast sequences provide detailed views of soft tissue, muscle, and bone involvement, while T2-weighted sequences reveal the characteristic high-flow vascular channels as flow voids (30,33). For dynamic flow analysis, time-resolved three-dimensional magnetic resonance angiography (3D-MRA) with contrast can be used. Advanced techniques such as Time-Resolved Angiography with Interleaved Stochastic Trajectories (TWIST-MRA) enhance temporal and spatial resolution, addressing some of the limitations of conventional 3D-MRA (33,34). Although TWIST-MRA has been extensively applied in intracranial AVMs, its clinical utility in extracranial AVMs requires further investigation (35).

Computed tomography angiography (CTA) is a debated tool in the diagnostic evaluation of AVMs. While it offers high spatial resolution and rapid image acquisition, its reliance on ionizing radiation and the potential need for multiple acquisitions pose significant drawbacks (34). Despite these limitations, CTA can provide detailed anatomical information in complex cases and aid in three-dimensional vascular reconstructions.

Digital subtraction angiography (DSA) remains the gold standard for evaluating the vascular anatomy and flow dynamics of AVMs. It offers unmatched detail in delineating the lesion's angioarchitecture, which is essential for classification systems that categorize AVMs based on specific arteriovenous connections (30,33,34). Additionally, DSA is particularly valuable for planning interventions, as it allows simultaneous diagnostic imaging and therapeutic procedures. However, its invasive nature and the associated risks of arterial catheterization and contrast administration necessitate cautious and judicious use.

Therapeutic Management

Effective management of AVMs requires a multidisciplinary approach in specialized centers, as there is no clear consensus on an optimal therapeutic strategy. Treatment is typically tailored to the lesion's angioarchitecture and the expertise of the treating team, with a primary approach combining endovascular embolization and surgical excision, as illustrated in **Fig 4**. Incomplete treatment can exacerbate lesion growth by activating angiogenic pathways, further complicating management. Despite emerging antiangiogenic therapies, extracranial AVMs remain among the most challenging vascular anomalies to treat. Even with aggressive interventions, recurrences are frequent and remission cannot be confirmed until at least five years post-treatment, and approximately 5% of cases recur even after 10 years(36).

Surgical treatment aims to achieve complete resection with clear margins, ensuring the nidus is entirely removed. It is generally indicated for localized lesions where complete excision does not result in significant functional or cosmetic sequelae(36,37). Some authors advocate staged surgical resections(37), but this approach remains controversial due to high recurrence rates. Preoperative embolization is a valuable adjunct, assisting in nidus delineation and reducing intraoperative blood loss, although it does not appear to significantly reduce recurrence(38). Wide resection margins are critical to minimizing recurrence, with rates ranging from 15.8% to 32.2%, depending on resection precision(39,40). Recurrence can reach as high as 85% in certain series(36,37), with incomplete excision and residual blood flow as key contributors(41). Postoperative reconstruction may be necessary to address functional or aesthetic defects, and some evidence suggests that free flaps may reduce recurrence, though this remains debated(42,43).

Endovascular therapy seeks to obstruct blood flow and destroy the nidus endothelium, which is critical to prevent revascularization. Simply blocking blood flow is insufficient and often leads to secondary revascularization. Proximal arterial ligation is not only ineffective but may complicate future access for additional treatments. Multiple staged treatments with short intervals between sessions are often required to reduce recurrence risk. Three main access routes are utilized: transarterial, transvenous, and direct transcutaneous nidus puncture. Transarterial access is most commonly used, while the transvenous approach is favored when arterial access is challenging or to avoid embolization outside the nidus(44). Preoperative embolization often employs agents such as N-butyl cyanoacrylate (NBCA) or glue to reduce intraoperative bleeding without destroying the lesion. The choice of embolic agents varies by physician or center, with ethanol being considered the most effective for nidus destruction, although its systemic toxicity necessitates caution. Four main categories of embolic agents are employed: particulate agents (e.g., microspheres), liquid sclerosing agents (e.g., ethanol), polymerizing agents (e.g., NBCA or Onyx®), and mechanical occlusive devices. Mechanical devices are typically avoided unless used in conjunction with other agents, as they often fail to destroy the endothelium(44). Angiographic improvements are reported in 80–100% of cases, but complete eradication is achieved in only 7–10%(37,44). Treatment efficacy largely depends on the physician’s expertise and the ability to thoroughly devascularize the lesion and destroy the nidus endothelium, often requiring multiple sessions(45).

Pharmacologic interventions are emerging as adjuncts to invasive treatments, with antiangiogenic agents showing promise (46). Agents, such as bevacizumab, which inhibits VEGF-A, have demonstrated limited efficacy in extracranial AVMs(47,48). Thalidomide, with its anti-VEGF and anti-inflammatory effects, has shown benefits in severe cases(49,50). MEK inhibitors, particularly trametinib, are emerging as promising therapies, with ongoing trials evaluating their efficacy(51-57). These agents target the hyperactive RAS/RAF/MEK/ERK pathway commonly involved in AVMs, and other inhibitors, such as cobimetinib, are currently being tested (e.g., COBI-AVM study, NCT05125471). mTOR inhibitors have also been tryed, but their efficacy appears limited, with sirolimus failing to show superiority over endovascular treatments alone(37,58). These agents may hold the most promise for AVMs with PTEN mutations, resulting in PI3K/AKT/mTOR hyperactivation, but further research is required.

Corticosteroids have been used to reduce inflammation and provide short-term relief but are limited by their side effects and the need for high doses(24). Matrix metalloproteinase inhibitors (MMPi) have been explored based on their potential to limit extracellular matrix remodeling, which is a key driver of pathological neoangiogenesis(59,60). Propranolol has shown limited efficacy, likely attributable to its ability to reduce blood pressure within the malformation rather than directly targeting endothelial cells(61).

Non-invasive therapies have been explored as alternatives or adjuncts to invasive treatments. Percutaneous interstitial sclerotherapy using agents such as bleomycin(62,63) or doxycycline(30) has shown promise, particularly in early-stage AVMs. However, these approaches often require multiple sessions and high cumulative doses, with long-term efficacy unclear. Laser therapy, such as Nd:YAG, has been employed for mucosal AVMs, but its limited penetration depth restricts its utility to superficial lesions(31). Laser therapy is generally combined with other treatments and is insufficient as a single approach.

Determining the timing of treatment remains a significant challenge in AVM management. While early intervention is suggested for lesions amenable to complete eradication, asymptomatic or minimally symptomatic AVMs may be monitored initially(2,36,37,44). This approach can be counterintuitive given the progressive nature of AVMs, but the decision to treat remains complex and highly individualized. Further research is required to guide the optimal timing and selection of treatment strategies for asymptomatic extracranial AVMs.

Future Prospects

The treatment of AVMs requires significant advancement in standardization. Due to the heterogeneous nature of AVMs, establishing standardized treatment protocols is only feasible if lesions are further subcategorized to allow for tailored care. Subclassification initiatives have been undertaken by ISSVA(5), with additional refinements proposed by the VASCERN-VASCA working group(6). Several classification systems have been previously developed(39,32,33), with the SECG system emerging as one of the most comprehensive and user-friendly frameworks(34). However, this system remains incomplete, and a revised proposal is currently in preparation(35) (Colletti et al., unpublished).

When evaluating an AVM, five critical questions must be addressed, as summarized in **Fig 5**: (1) is the AVM part of a syndrome, (2) where is it precisely located and which tissues are involved, (3) what is the underlying angioarchitecture, (4) is the causative genetic mutation known , and (7) is the lesion symptomatic or has the lesion recently progressed ? In syndromic AVMs, the initial work-up should be expanded. For example, CM-AVM can be associated with CNS and spinal AVMs and may be inherited. PKWS often involves limb length discrepancies that need orthopedic follow-up as it may require intervention. In PHTS, additional lesions and cancer screening are recommended. In CAMS and SAMS, CNS fast-flow lesions must be excluded. Precise anatomical location and tissue involvement are critical for guiding therapeutic decisions. The feasibility of complete resection should be evaluated alongside the extent of tissue defect that would require reconstruction. Angioarchitecture and anatomical location inform the choice of endovascular access routes and embolic agents. Knowledge of the causative genetic mutation may enable the use of targeted therapies or influence prognosis. For instance, in the head and neck region, *KRAS*-mutated AVMs seems to exhibit more aggressive behavior, maybe warranting early treatment. If a lesion demonstrates recent or rapid progression, timely intervention is generally recommended.

In recent years, antiangiogenic medications, largely derived from oncology field, have led new possibilities for AVM management. Thalidomide and trametinib have demonstrated clinical efficacy(49, 50, 52), and other MEK inhibitors have also been explored(51, 48). However, as standalone therapies, antiangiogenic agents do not offer a definitive cure. The future likely lies in combining invasive interventions with antiangiogenic therapies (**Fig 4**). The underlying rationale is that such medications could mitigate abnormal EC responses to hypoxia, particularly during the postoperative period. Combining preoperative embolization, complete surgical excision, and (neo-)adjuvant thalidomide has shown promise in reducing early postoperative recurrence rates. In a prospective case series of fourteen patients undergoing complete surgical excision with preoperative embolization, all received adjuvant thalidomide for an average of 9.9 months postoperatively, and eleven of these patients also received neoadjuvant thalidomide for an average of 3.7 months. Over three years of follow-up, only one recurrence was observed, which occurred in a patient who had not received neoadjuvant thalidomide. No postoperative complications were noted, despite thalidomide's antiangiogenic properties(64).

With a similar goal of suppressing abnormal hypoxic responses in AVMs, the effects of embolization could potentially be enhanced by combining it with antiangiogenic medications. While a few unpublished cases have reported successful combinations without post-

interventional complications, it remains unclear whether this approach is superior to interventional radiology alone. Further research is needed to determine whether this combination therapy offers enhanced efficacy compared to conventional approaches.

Conclusion

AVMs represent a complex subset of vascular anomalies, characterized by their progressive behavior and significant clinical heterogeneity. Advances in molecular genetics, particularly the identification of RAS/RAF/MEK/ERK pathway mutations, have deepened our understanding of their physiopathology and opened new avenues for targeted therapies. However, significant challenges remain in classification, and management. The multidisciplinary management of AVMs requires a combination of detailed diagnostic imaging, individualized surgical and endovascular interventions, and emerging pharmacologic therapies. Despite these advancements, treatment outcomes remain suboptimal, with high recurrence rates highlighting the need for complete nidus removal and ongoing innovations in therapeutic strategies. Antiangiogenic medications, particularly MEK inhibitors and thalidomide, have shown promise as adjuncts to invasive treatments. The combination of preoperative embolization, complete surgical excision, and adjuvant pharmacologic therapies has demonstrated encouraging preliminary results, warranting further investigation. Standardization of treatment remains a critical goal, necessitating improved classification systems that integrate clinical, anatomical, and genetic factors. Future prospects lie in integrating advanced molecular diagnostics with innovative therapeutic combinations, bridging invasive and pharmacologic modalities. Ongoing clinical trials and multicenter collaborations are essential to refine these approaches and establish evidence-based guidelines. By aligning genetic insights with clinical expertise, the field is poised to deliver more effective, patient-centered care for this challenging and heterogeneous group of vascular anomalies.

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Figure legends

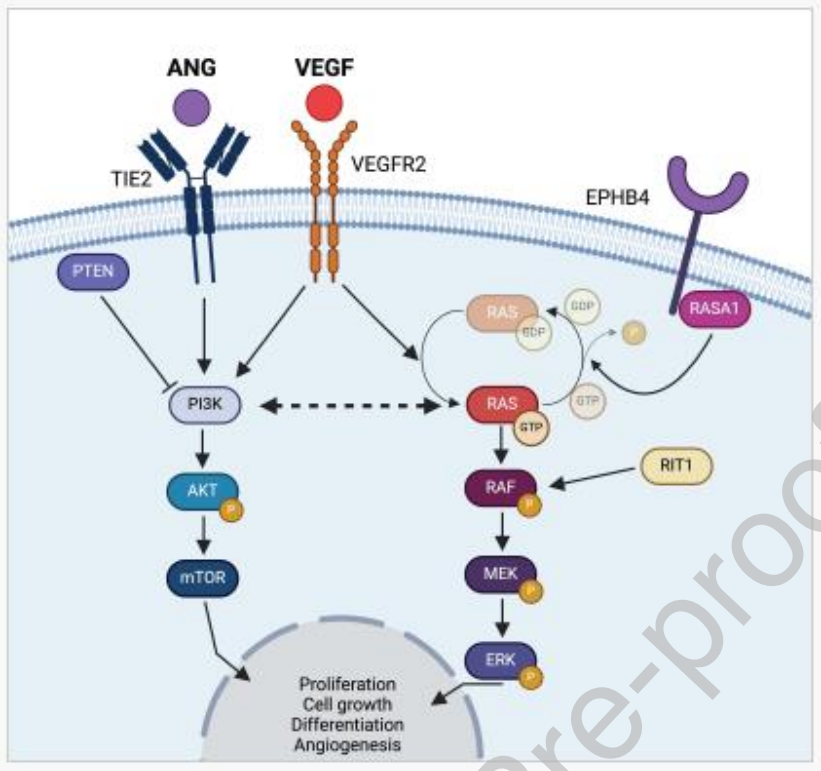

Figure 1 : Representation of the main mollecular pathways involved in arteriovenous malformations. AKT : Protein kinase B; Ang : Angiopoietin; EPHB4 : Ephrin type-B receptor 4; ERK : Extracellular regulated kinase; GDP : Guanosine diphosphate; GTP : Guanosine triphosphate; MEK : Mitogen activated protein kinase(MAP)-extracellular signal-regulated kinase; mTOR : Mammalian target of rapamycin; P : Phosphate; PI3K : Phospho-inositol kinase 3; PTEN : Phosphatase and tensin homolog; RAF : Rapidly accelerated fibrosarcoma kinase; RAS : Rat sarcoma virus protein; RASA1 : RAS p21 protein activator 1; RIT1 : Ras like without CAAX 1; VEGF : Vascular endothelial growth factor; VEGFR2 : VEGF-receptor 2 (illustration created with BioRender).

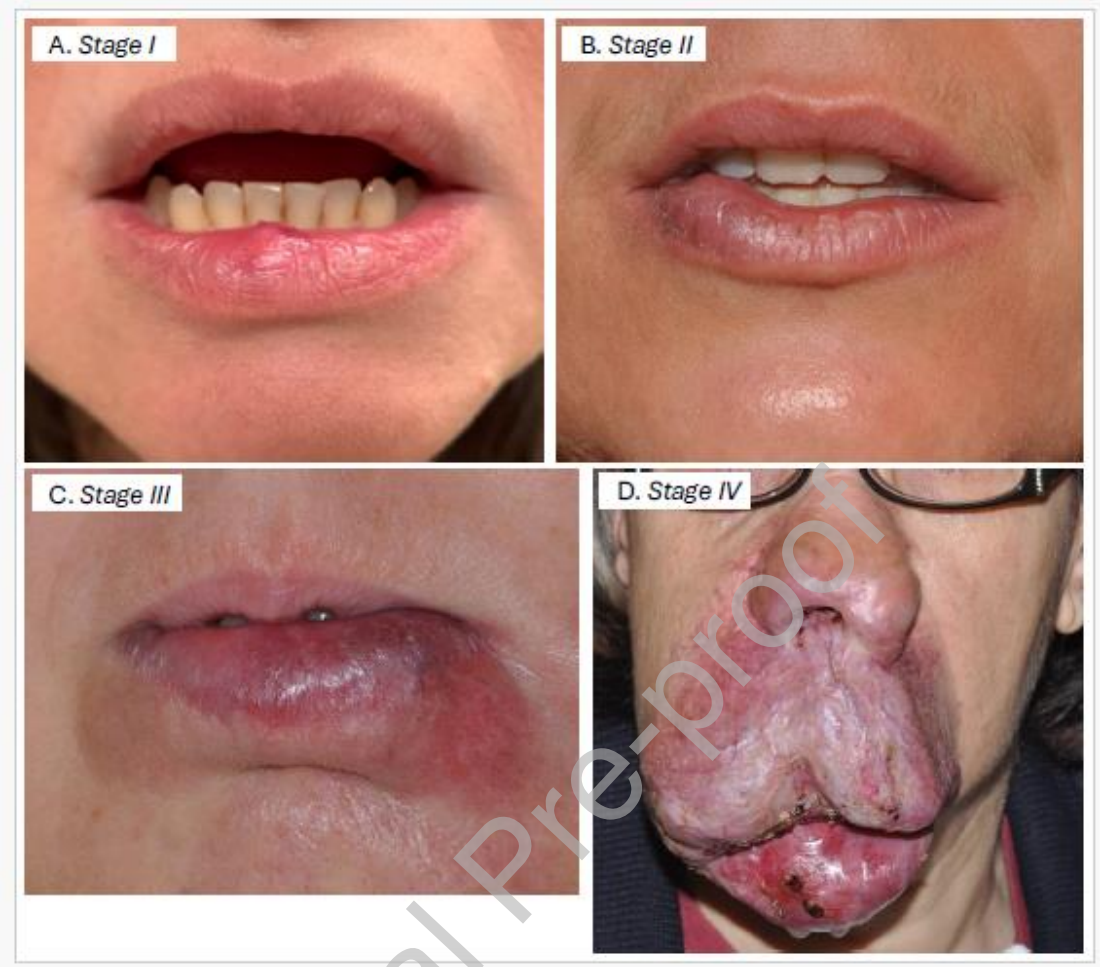

Figure 2 : Clinical illustration of the four Schöbinger stages. Stage I AVM of the median lower lip (A.). Stage II AVM of the right lower lip (B.). Stage III AVM of the complete lower lip, with ulceration sequellae of the left lwer lip (C.). Stage IV AVM of the middle and lower face (D.).

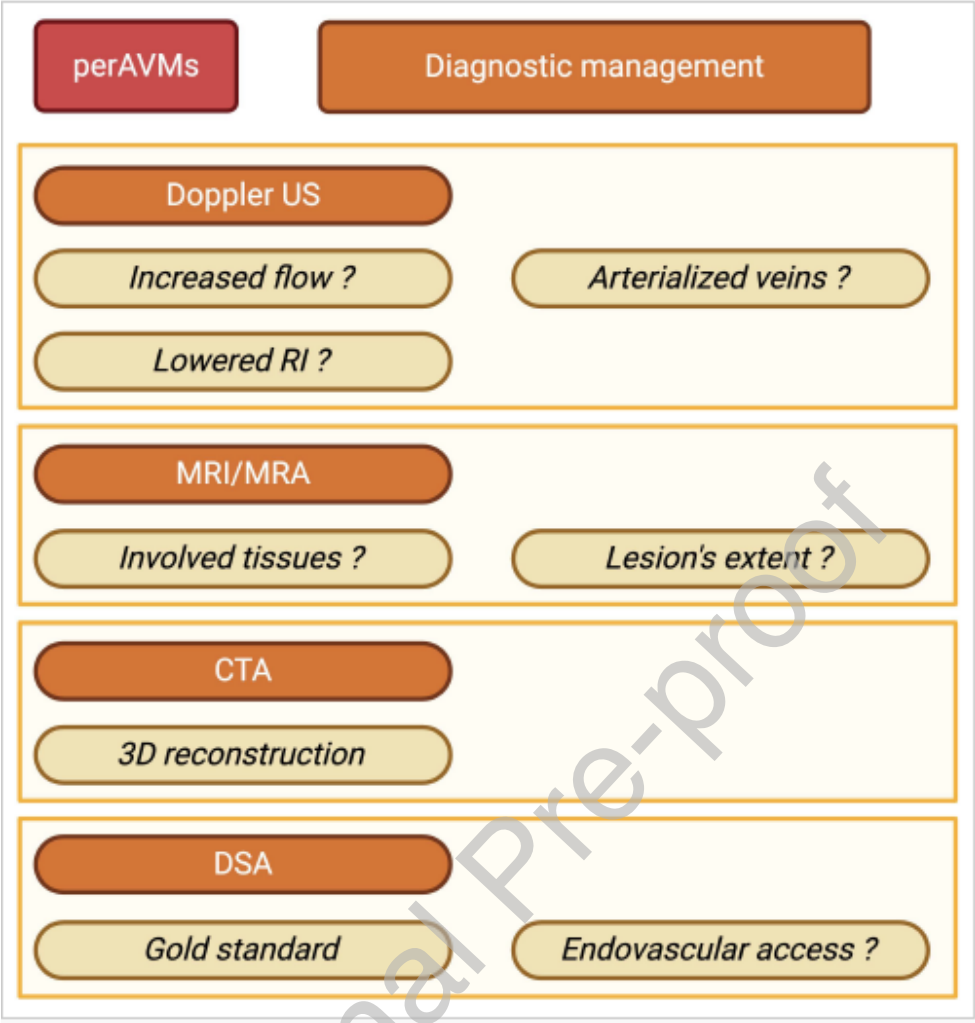

Figure 3 : Schematic representation of the different imaging modalities used as a diagnostic work-up in peripheral arteriovenous malformations. CTA : computed tomography angiography; DSA : digital substraction angiography; MRI : magnetic resonance imaging; MRA : magnetic resonance angiography; PAVMS : peripheral arteriovenous malformations; RI : resistance index; US : ultrasound.

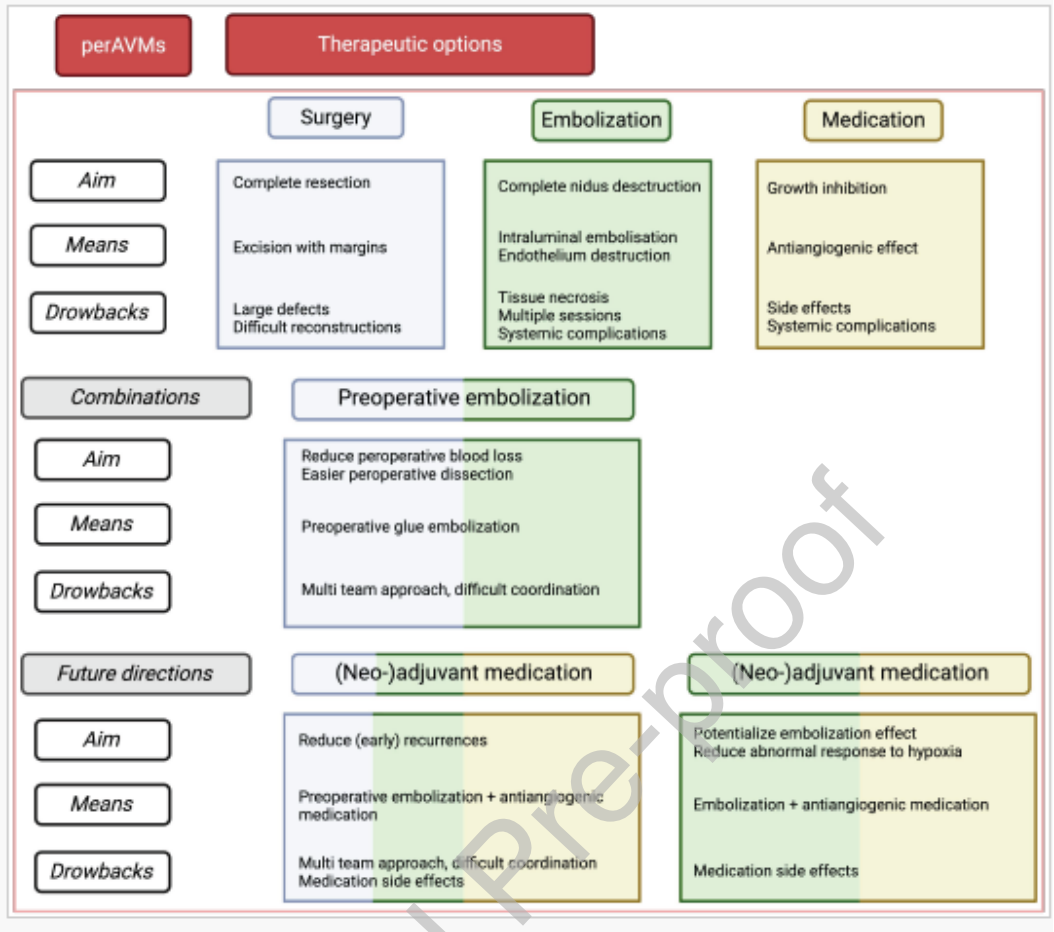

Figure 4 : Schematic representation of the different treatment modalities available for peripheral arteriovenous malformations (PAVMs).

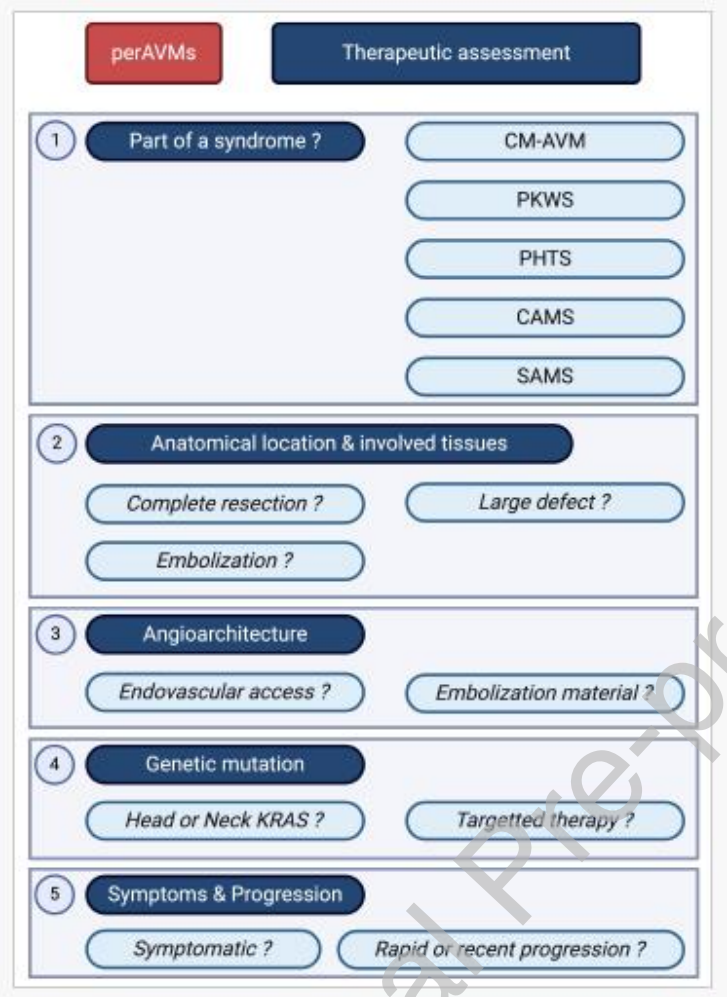

Figure 5 : Schematic representation of the five questions that should be adressed before treating a peripheral arteriovenous malformation. CAMS : cerebrofacial arteriovenous metameric syndrome; CM-AVM : capillary-malformation – arteriovenous malformation; PAVMs : peripheral arteriovenous malformation; PKWS : Parkes-Weber syndrome; PHTS : *PTEN*-associated hamartoma tumor syndrome; SAMS : spinal arteriovenous metameric syndrome.

Credit roles:

Julien Coulie: Writing - Original Draft Preparation.

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Laurence M Boon: Writing – Review and Editing, Project funding and management.

Conflicts of Interest

All authors declare that they have no conflicts of interest